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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/603,448	06/26/00	THOMAS S	M&G 10552.26

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EXAMINER	
FREDMAN, J	

ART UNIT	PAPER NUMBER
1655	5

DATE MAILED: 04/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/609,448	Thomas
Examiner	Group Art Unit
Jeffrey Fredman	1655

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-56* is/are pending in the application.

Of the above, claim(s) *28-55* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27 and 56* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-27 and 56, drawn to screening for mutagens, classified in class 435, subclass 6.

II. Claims 28-54, drawn to recombinant host cells, classified in class 435, subclass 252.3.

III. Claim 55, drawn to a protein, classified in class 530, subclass 350.

2. The inventions are distinct, each from the other because of the following reasons: Inventions in Group II and in Group I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the expression vectors can be used for protein synthesis, for nucleic acid purification, for DNA amplification assays or for DNA detection assays, as well as the mutagen method of Group I. The host cells can be used for protein synthesis, for in situ hybridization methods, for isolation of nucleic acids or for the mutagen method of Group I.

3. Inventions in Groups I and II and in Group III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the

instant case the different inventions are unrelated because the protein is chemically and structurally different than the nucleic acids of Group II or the methods of Group I and the protein is not used by the method of Group I.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Mark Skoog on April 3, 2001, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-27 and 56. Affirmation of this election must be made by applicant in replying to this Office action. Claims 28-55 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). For example, the sequences in figure 13. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. There is no CRF and no paper copy of the sequence listing.

Claim Rejections - 35 USC § 112

7. Claims 4 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is the scope of "variant" as applied to SOS gene or to "mutant sensitive gene" in claims 4 and 6. Claim 6 is particularly unclear since "mutant sensitive gene" is different than "mutagen sensitive gene" and it is unclear what distinction is meant by the change in terminology. With regard to the term variant, it is unclear what limitation this term imposes since any particular SOS gene might be termed a variant of another SOS gene. Similiarly, any particular mutant sensitive gene might be termed a variant of another such gene. Thus, it is unclear how these terms further limit the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 1-18 and 21-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Justus et al (Mutagenesis (1999) 14(4):351-356).

Justus teaches a method of determining a mutagen comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a green fluorescent protein

operably linked to a mutagen sensitive gene such as umuC which is an SOS gene (page 351, column 2), b) monitoring a host cell preparation for fluorescent protein by diluting the host cells which may be either in stationary phase or in logarithmic growth and incubating the host cells at 37C with shaking (page 352, column 1), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into saline (page 352, column 1), c) determining a mutagen when an amount of fluorescent protein meets or exceeds a predetermined threshold value (page 352, figure 2 and column 2). Justus further teaches detection using a range of concentrations of the test compound (page 352, figure 2), as well as measurement in 96 well plates at excitation wavelengths of 485 nm and detection at 510 nm (page 352, column 1). Justus teaches using analyzing a change in the shape of the data comparing a control cell with the test compound as shown on page 352, figure 2 and column 2.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-9, 11-14, 16-18, 21-23 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Justus et al (Mutation Research (1998) 398:131-141) in view of Chalfie et al (Science (1994) 263:802-804)

Justus teaches a method of determining a mutagen comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a reporter protein operably linked to a mutagen sensitive gene such as umuC which is an SOS gene (page 133, column 1), b) monitoring a host cell preparation for reporter protein by diluting the host cells which are in logarithmic growth and incubating the host cells at 37C with shaking (page 134, column 1), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into phosphate buffer (page 134, column 1), c) determining a mutagen when an amount of reporter protein meets or exceeds a predetermined threshold value (page 134, column 2). Justus further teaches detection using a range of concentrations of the test compound (page 137, figure 6). Justus teaches using analyzing a change in the shape of the data comparing a control cell with the test compound as shown on page (page 137, figure 6 and page 134, column 2).

Justus does not teach the use of green fluorescent protein as the reporter gene, nor the specific wavelengths of excitation and detection.

Chalfie teaches the use of the green fluorescent protein as a reporter gene and teaches that the protein is excited at 485 nm and detected at 509 nm (page 802, column 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Justus using a luciferase reporter gene and replace the luciferase reporter gene with the GFP protein of Chalfie since Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly

luciferase and bacterial luciferase. Because such methods require exogenously added substrates or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase reporter protein used by Justus since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light.

12. Claims 1-18, 21-27 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr (U.S. Patent 5,589,337) in view of Chalfie et al (Science (1994) 263:802-804).

Farr teaches a method of determining a mutagen (column 5, ines 8-15) comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a reporter protein operably linked to a mutagen sensitive gene (column 19, line 40 to column 20, line 19 and column 29, example 7) such as dinD which is an SOS gene (column 7, lines 3-15), b) monitoring a host cell preparation for reporter protein by diluting the host cells which are in logarithmic growth or stationary growth and incubating the host cells at 37C with shaking (column 14, lines 5-65), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into minimal media (Column 14, lines 10-12), c) determining a mutagen when an amount of reporter protein meets or exceeds a predetermined threshold value (columns 29-31, example 7). Farr further teaches detection using a range of concentrations of the test compound (column 30,

table 1). Farr teaches using analyzing a change in the shape of the data comparing a control cell with the test compound as shown on (figure 9-12). Farr further teaches identification methods to detect antimutagens (column 31, example 8). Farr expressly teaches screening in 96 well microtiter plates (column 31, line 27).

Farr does not teach the use of green fluorescent protein as the reporter gene, nor the specific wavelengths of excitation and detection.

Chalfie teaches the use of the green fluorescent protein as a reporter gene and teaches that the protein is excited at 485 nm and detected at 509 nm (page 802, column 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Farr using a luciferase reporter gene and replace the luciferase reporter gene with the GFP protein of Chalfie since Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly luciferase and bacterial luciferase. Because such methods require exogenously added substrates or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase or galactosidase reporter protein used by

Farr since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light.

13. Claims 1-27 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr (U.S. Patent 5,589,337) in view of Chalfie et al (Science (1994) 263:802-804) and further in view of Mitchell et al (Mutation Research (1986) 159:139-146).

Farr in view of Chalfie teach the limitations of claims 1-18, 21-27 and 56 as discussed above. Farr in view of Chalfie do not teach the use of the Kolmogorov Smirnov test with selection of a P value less than .05.

Mitchell teaches the use of a Kolmogorov Smirnov test for the analysis of data regarding the ability of mutagens to effect a reporter system and show a number of Significance levels including $P<.05$ (page 142, table 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Farr in view of Chalfie with the use of the Kolmogorov Smirnov statistical test of Mitchell since Mitchell states "It was concluded that the non-parametric Kolmogorov-Smirnov two-sample test was the most reliable method of analysis (abstract)". An ordinary practitioner would have been motivated to use the Kolmogorov-Smirnov test because it was a normal statistical analysis tool which was identified as the most reliable in determining which mutagens were statistically significant.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Group 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

April 4, 2001